Conjugated Estrogens and Breast Cancer Risk in Women [1,2]

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ABSTRACT—The relationship between conjugated estrogen(s) (CE) and breast cancer was investigated by the examination of the records of 345 women with newly diagnosed breast cancer and 611 healthy controls belonging to a prepaid health plan. Use of CE was associated with a 40% elevation in risk [relative risk (RR) = 1.4; 95% confidence interval = 1.0–2.0]. The RR was 1.3 for menopausal women with intact ovaries and 1.5 for those with ovaries removed. There was statistically significant evidence of a dose-response relationship with the three measures of dose evaluated. RR's rose to about twofold for women with 10 or more CE prescriptions noted in their charts, for those with 5 years or more between their first and last prescription, and for those with a usual daily dose of 1.25 mg or more. The RR associated with having ever used CE and with long-term use was highest among those women with a family history of breast cancer. These data support the hypothesis that long-term use of CE is associated with increased breast cancer risk.—JNCI 1981; 67:815-820.

Clinical reports, animal experiments, and the probable role of endogenous estrogens in modifying breast cancer risk have prompted concern over the potential carcinogenicity of estrogenic medications (*1, 2*). Observations of a substantially increased risk of cancer of another estrogen-sensitive organ, the endometrium, following the use of estrogens have heightened this concern (*3-14*). A number of case-control and follow-up studies have not identified an excess breast cancer risk in association with the use of these agents (*15-29*). However, one follow-up study raised the possibility of an increased breast cancer risk among long-term users of CE (*30*), and a recent case-control study yielded a similar finding (*31*). All of the studies to date have been hampered by small numbers of long-term users. To test the hypothesis of excess breast cancer risk among long-term users of CE, we conducted a case-control study in a large prepaid health plan.

METHODS

The tumor registry of the KFHP of Portland, Oregon, identified all cases of breast cancer occurring from January 1969 through December 1975 among women enrolled in the health plan. The records of all of these women were reviewed to verify the diagnosis and the fact that the case was newly incident in the KFHP during the study period. While this review was under way, a computerized 5% random sample of all members of the KFHP, routinely maintained for other purposes since 1966, was used to draw a stratified random sample of controls, stratified to the distribution of a random sample of verified cases on the basis of age (2-yr interval), year of entry into the health plan, and duration of health plan membership (to the date of diagnosis). The control series was chosen to be twice the size of the anticipated case series. Three hundred and eighty eligible cases (all histologically confirmed) and 674 controls were identified and comprise the initial study population. The lack of a complete 2:1 group matching ratio (controls:cases) was not due to a lack of potential controls in any strata but due to more verified cases resulting from the record review than we had anticipated from our sample.

Oophorectomy at a young age is associated both with a lower risk of breast cancer and a greater likelihood of estrogen use as replacement therapy (*1*) and therefore is a potential confounding factor to the evaluation of breast cancer risk among estrogen users. Because of this, women who had a surgical menopause at a relatively young age (<45 yr) were only included if we had information on ovarian status. This resulted in the exclusion of 35 cases and 63 controls who had a surgical menopause under age 45 *before* they had become health plan members and, therefore, for whom we had no operative reports concerning ovarian status.

For each study subject a reference date was designated; this date was 3 months prior to the date of diagnosis for the cases and for the controls was 3 months prior to the date of diagnosis of the cases used to define the strata for control selection. Only drug exposures noted in the women's records *prior to* this reference date were abstracted by experienced medical record technicians, who were also unaware of the case or control status of any particular record. This proce-

ABBREVIATIONS USED: CE = conjugated estrogen(s); CI = confidence intervals; DES = diethylstilbestrol; KFHP = Kaiser Foundation Health Plan; RR = relative risk(s); RR_M = maximum likelihood estimates of RR.

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dure was followed to avoid the possibility of biased recording of drug exposure due to the workup for a breast lump.

The information abstracted included breast cancer risk indicators and all therapeutic drugs taken by the patient and noted in the outpatient chart. For this study, the measures of exposure to estrogens were these notations of use in the chart. The vast majority of these notations referred to prescriptions written by a physician at that time, but they also included occasional notations concerning use prior to KFHP membership. The number of such notations of prescriptions will be less than the actual number of prescriptions, since it will exclude refills not requiring a physician's consent. Therefore, these crude estimates of extent of exposure may lead to some random misclassification of "true" dose. The degree to which this occurs would, as in any such misclassification, lead to underestimates of true dose-response relationships. However, the number of such notations in the chart has been shown to be a reliable relative index of use (i.e., the more notations, the more use) (*3-14*). The early studies of CE use and endometrial cancer used such indices of exposure. The RR from these studies have been confirmed subsequently by studies that have used a variety of more sophisticated techniques for dose estimation (e.g., personal interviews, prescription linkage, and physician validation).

The estimate of strength of an association used was the RR as estimated from a case-control study by the odds ratio (*32*). The RR indicates the risk of breast cancer among those exposed to the factor under study relative to the risk among those not exposed. Where appropriate, the estimates of RR were controlled for the influences of other risk factors by stratification of the data on these variables and development of summary RR_M across these strata along with the 95% CI for these RR_M (*33*).

Information in the chart covering breast cancer risk indicators was derived from standardized forms used at the time of routine physical examinations, physicians' descriptions of the patient, or records of procedures actually performed in the health plan. Definitions of most of these variables are self-explanatory. Menopause was defined as the permanent cessation of menstruation.

The test of the statistical significance of the difference of an RR from that of 1.0 (no association) was the chi-square for a single contingency table and the Mantel-Haenszel summary chi-square when the data were controlled for other variables (*34*). The test for statistical significance of a trend over multiple levels of an exposure variable was the chi-square for linear trend in the case of a single table and its analog, the Mantel extension of the Mantel-Haenszel procedure, when summarizing over several tables (*35*).

Linear logistic regression analyses were also utilized to obtain estimates of RR_M while simultaneously controlling for a number of potential confounding factors (*36*).

RESULTS

The average age of the 345 women with breast cancer was 57.3 years, and their average duration of health plan membership was 8.6 years. This corresponded well to the average age of the 611 control women (57.7) and their average duration of membership (8.8), indicating the success of the group-matching procedure.

Preliminary analysis addressed the relationship between breast cancer risk and a number of previously identified breast cancer risk indicators. The number of individuals for whom this information was unknown varied from a low of 12-13% for weight and parity to a high of 44% for age at menarche. However, when such information was restricted to that recorded before the reference data for each patient, the percentage of cases with unknown values was similar to the comparable percentage for the controls. There was a statistically significant increased RR associated with a family history of breast cancer, prior surgery for benign breast disease, and a relatively old age of a subject when she had her first child. In addition, estimates of RR were lower for nonwhites compared to whites, lower for patients with a bilateral oophorectomy compared to intact women, lower for women having undergone menarche at 12 years of age or over, and lower for women having undergone menopause prior to age 40. While each of these latter associations was consistent with previous observations, none were statistically significant ($P>0.05$).

Two hundred and eleven cases and 389 controls had no mention of any use of estrogens in their charts. These women form the referent group for the calculation of all of the RR concerned with estrogen use.

Twenty-five cases and 67 controls had had a prescription for DES (RR=0.7; CI=0.4-1.1). The apparently diminished risk was limited to those women with only one such prescription (RR=0.5; CI=0.3-1.1). The RR for women with multiple prescriptions was 0.9 (CI=0.5-1.6).

One hundred and thirteen cases (35%) had a mention of CE use in their charts compared to 160 (29%) of the controls (RR=1.3; CI=1.0-1.7). Thirty-four percent of these cases and 38% of these controls had no specific indication for first use mentioned. For 50% of exposed cases and 47% of exposed controls, menopause or menopausal symptoms were specifically indicated as the reason for prescription. Four percent of both cases and controls were treated because of atrophic vaginitis, and another 12% of cases and 11% of controls had a wide variety of other indications mentioned.

The percent of women exposed to CE varied by menopause status. The percent of control women exposed to CE ranged from 10% for those who were premenopausal (all women >40 yr who used CE for "menopausal symptoms"), to 42% for women having a natural menopause, and to 73% for women who had become menopausal via a bilateral oophorectomy. After control for type of menopause, the RR_M associated with CE use was 1.4 (CI=1.0-2.0). The RR of

breast cancer (and CI) for having ever used CE was 1.7 (0.7-4.0) for premenopausal women, 1.3 (0.8-2.1) for menopausal women with intact ovaries, 1.5 (0.3-6.6) for women having had a bilateral oophorectomy, and 1.3 (0.7-2.6) for those whose type of menopause or menopause status was unknown. The higher risk among premenopausal women appeared to be an age effect rather than a menopause status effect. While there was no significant or consistent variation in RR by age, young women (<50 yr) had a higher RR associated with CE use, an elevation that was similar for premenopausal and postmenopausal women. The RR_M for CE use among women under age 50, controlled for menopause status, was 2.3 (1.1-4.9).

The amount of CE exposure was evaluated by the number of prescriptions of CE use noted in the chart, the number of years between the first and last prescription for those with more than one, and the usual dose (milligrams) of medication prescribed. Numbers of cases and controls along with crude and maximum likelihood estimates of RR for these measures are given in table 1. There was a consistent and significantly increasing trend in RR with increasing use of CE, rising to 1.7-1.8 for those with 10 prescriptions or more and those with 5 years or more between first and last prescription. The numbers of prescriptions and the interval between the first and last one were so highly correlated that no assessment of the independent contributions of these two measures of use could be made. The RR also increased significantly with increasing dose of CE usually used, rising to 1.8 for those whose usual daily dose was 1.25 mg or greater. Number of prescriptions and usual dose were not correlated (e.g., 36% of those using ≤0.625 mg and 33% of those using ≥1.25 mg had had five prescriptions or more). However, the trend in RR by number of prescriptions was derived primarily from those whose usual dose was 1.25 mg or more. Among these women the RR was 1.4 for those with one to four prescriptions and 2.3 for those with five or more.

TABLE 1.—*Cases, controls, and RR of breast cancer according to the number of prescriptions for CE noted in a patient's chart, the number of years between first and last prescription, and the usual dose of CE*

Parameter	Cases	Controls	RR[a]	RR_M[b]
No. of prescriptions				
None	211	389	1.00	1.00
1	22	41	1.0	1.1
2-4	45	64	1.3	1.3
5-9	29	36	1.5	1.8
≥10	17	19	1.7	1.8
		$\chi_1^2=6.18$[c] ($P=0.013$)		
Years between first and last prescription				
None	211	389	1.00	1.00
≤4	55	73	1.4	1.4
≥5	36	46	1.4	1.7
		$\chi_1^2=5.22$[c] ($P=0.022$)		
Usual daily dose, mg				
Nonusers	211	389	1.00	1.00
<1.25	20	28	1.3	1.4
≥1.25	74	92	1.5	1.8
		$\chi_1^2=7.78$[c] ($P=0.005$)		

[a] RR=crude RR, relative to a risk of 1.00 for those having never used estrogens.
[b] Controlled for type of menopause.
[c] χ^2 test for linear trend in the RR_M.

As was true for the comparison of ever versus never used, there were some differences in the RR for long-term users by menopause group. For example, the RR for 10 or more prescriptions was 4.7 for premenopausal women, 3.7 for menopausal women having had a bilateral oophorectomy, 1.4 for women with a natural menopause, 0.8 for women with a surgical menopause but intact ovaries, and 2.0 for women whose menopause status or type was unknown. On the basis of the numbers of observations in each stratum, all of these estimates are consistent with the overall summary RR (P-value for heterogeneity=0.53). However, the pattern of differences by strata may be noteworthy.

While the percentage of women exposed to conjugated estrogens is quite high, it is still possible that some of the "unexposed" could have received estrogens while not in the KFHP. Restricting the nonusers to only those who had been in the KFHP for 10 years or more (the ones whose lack of exposure was best documented) yielded estimates of RR_M slightly higher than those presented above, e.g., 1.6 (CI=1.0-2.4), for ever using CE and 2.0 for those with 10 prescriptions or more noted in their charts.

The association of breast cancer risk with CE use was not confounded by age, race, duration of plan membership, parity, age at first birth, age at menopause, weight, previous history of benign disease, or use of other female hormone preparations (DES, oral contraceptives, and progestins) because control for these variables did not substantially alter the estimates of RR. In addition, there was no statistically significant effect modification of the CE association by any other risk factor. However, the estimates of RR did vary by level of several other breast cancer risk factors (table 2). While the trends in risk by numbers of prescriptions were somewhat variable, the RR for heavy users seemed higher for multiparous women, for those with a young age at first live childbirth, for those without benign breast disease, and for those with a family history of breast cancer.

Potential confounding was also controlled with the use of a linear logistic regression analysis with parity, age at first birth, family history of breast cancer, prior benign breast disease, duration of plan membership, age, and menopause status entered as potential confounding variables. The estimate of the RR_M associated with the use of CE from this analysis was 1.4 (0.9-2.0). The corresponding estimates of RR_M for numbers of CE prescriptions were 0.9 for one prescription, 1.3 for two to four, 1.7 for five to nine, and 1.9 for 10 prescriptions or more. All of these estimates are virtually identical to those obtained from the contingency table analyses.

TABLE 2.—*RR_M[a] of breast cancer and numbers of exposed cases[b] according to the number of prescriptions for CE by level of other breast cancer risk indicators*

Breast cancer risk indicator	No. of prescriptions for CE		
	None	<5	≥5
Parity			
0	1.0 (25)	1.3 (5)	1.4 (6)
1–2	1.0 (93)	1.4 (39)	1.5 (20)
≥3	1.0 (81)	0.7 (20)	1.9 (20)
Age at first birth, yr			
<20	1.0 (11)	1.2 (5)	4.3 (5)
20–24	1.0 (52)	0.9 (16)	1.0 (14)
25–29	1.0 (38)	0.7 (13)	2.7 (14)
≥30	1.0 (27)	2.3 (14)	1.9 (6)
Prior benign breast disease			
No	1.0 (166)	1.2 (47)	1.6 (30)
Yes	1.0 (45)	0.8 (20)	1.1 (16)
Family history of breast cancer			
No	1.0 (184)	1.2 (60)	1.6 (37)
Yes	1.0 (27)	0.7 (7)	3.9 (9)

[a] Controlled for type of menopause. RR are all relative to an RR of 1.00 for those having never used estrogens, at each level of the other breast cancer risk indicator.
[b] Numbers of exposed cases are *in parentheses.*

DISCUSSION

This study supports the hypothesis of increased breast cancer risk among long-term users of CE. The RR rose to approximately twofold among long-term users, similar to the estimates previously published (*30, 31*). As noted, these recent studies are apparently at odds with the conclusions of a variety of earlier studies. Possible explanations for this have been described in detail elsewhere (*2, 37*).

Previous evaluations of the RR associated with CE use among subgroups of women defined in terms of the presence of other breast cancer risk factors have been few and have yielded conflicting evidence of effect modification. The RR associated with CE use has been reported to be higher among women having had a bilateral oophorectomy and among those with a prior history of benign breast disease (*30, 38*). However, a recent study found a higher risk associated with CE use among intact compared to oophorectomized women (*31*). Evidence of synergy between breast cancer risk factors and oral contraceptives has also been reported (*39, 40*). In the current study the estimate of RR associated with CE use, particularly long-term use, was greater for those who had had a bilateral oophorectomy than for those whose ovaries were still intact (3.7 vs. 1.4). While not statistically significant, this difference may be noteworthy. Since oophorectomized women have a low base-line risk, the addition of the same amount of estrogen-associated disease would appear relatively much greater in them compared to women with intact ovaries. In fact, these data suggest that the use of CE by oophorectomized women brings their breast cancer risk from the markedly reduced level for those not replaced to the same level of risk as women having undergone a natural menopause. With respect to other breast cancer risk factors, long-term CE use was associated with a particularly high RR among the young, among multiparous women, among those who were relatively young when they had their first child, and among those without a history of benign breast disease. Not one of these differences was statistically significant, but the pattern is consistent with that seen for ovarian status, i.e., a higher RR among those women with a lower base-line risk. The only exception to this pattern was the evidence of synergy between CE use and a family history of breast cancer, where the RR associated with five prescriptions or more for CE was 1.6 for those without a positive family history and 3.9 for those with one.

The lack of excess risk among long-term users of DES may simply be due to chance, since we had relatively few such women. However, this is an issue that deserves further scrutiny and is one of the subjects being addressed by an extension of this study to other prepaid health plans.

The consistency of the information on risk indicators with what is known about breast cancer (*1*) and the consistency of the RR associated with long-term CE use with other recent reports (*30, 31, 38*) have increased our confidence in the reliability of these data for assessment of long-term drug effects. However, explanations of the association with CE other than causality need to be considered. The characteristics of the study design have minimized many potential sources of bias. The cases were unselected, representing all of the incident cases in a defined population. The controls were a random sample of the population from whom the cases arose. The information on exposure to CE was recorded prior to the onset of the disease, and the individuals abstracting this information were unaware of which charts were from cases and which ones were from controls. In addition, information on breast cancer risk indicators was available on most subjects, allowing assessment of and control for confounding and effect-modifying influences.

While access to medical care is similar for members of the health plan, those women destined to become cases might, for some unknown reason, be greater users of the available care than those women who do not develop the disease. If this were so, then the cases might have had a greater opportunity to have any drug prescribed. There is evidence that such a theoretical bias does not exist. As noted, the percentage of women for whom various breast cancer risk factors noted in the chart prior to the reference date was unknown was similar for cases and controls. In addition, for Valium, a commonly prescribed drug chosen at the start of the study as a "control" drug, the overall RR was 0.7 (CI=0.5-1.0). With the use of the same categories for numbers of prescriptions of Valium as were used in the CE analyses, no individual RR was over 1.0.

Some criticisms of the studies associating estrogen use with endometrial cancer have suggested the possibility of another type of medical care-related ascertainment bias (i.e., earlier detection due to increased

medical surveillance of estrogen users) (*10*). Such a bias has been shown to be an unlikely explanation for the increased risk of endometrial cancer among estrogen users (*6, 14, 41*), and it is even less likely for breast cancer. The diagnosis of breast cancer is not dependent on any other drug-related effect, such as abnormal bleeding. Acute adverse breast reactions, such as engorgement, tenderness, or stimulation of growth of a subclinical tumor might lead to earlier identification of a breast lump. However, such enhanced detection should then occur soon after the initiation of therapy and would not explain the findings of this study, which relate to increased risk among long-term users after a considerable latent period.

Another explanation of the association with CE is that the excess risk of breast cancer is associated with the type of woman for whom estrogens are prescribed (i.e., those with menopausal symptoms). There is little support for this from previous epidemiologic investigations of breast cancer. However, more evidence should come from investigations among populations with varying exposure rates (i.e., varying criteria for the severity of symptoms requiring treatment).

Although the data support the hypothesis that long-term use of CE is related to an increased risk of breast cancer, the excess risk in epidemiologic terms is small (40% overall), and the CI around most of the risk estimates are wide. In addition, explanations of the association other than causality cannot be entirely ruled out. A final decision about the likely causality of the association will depend on results of a number of studies with different designs conducted in diverse population groups. While awaiting such studies, it seems prudent for the physician to assume that long-term use of CE preparations may increase breast cancer risk.

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